General

Guideline Title

Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children.

Bibliographic Source(s)

Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, Chong S, Colletti RB, Casswall T, Elitsur Y, Guarner J, Kalach N, Madrazo A, Megraud F, Oderda G, H pylori Working Groups of ESPGHAN and NASPGHAN. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):230-43. [147 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Gold BD, Colletti RB, Abbott M, Czinn SJ, Elitsur Y, Hassall E, Macarthur C, Snyder J, Sherman PM. Helicobacter pylori infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 2000 Nov;31(5):490-7.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): The following key points summarize the content of the guideline recommendations. Refer to the full text for additional information, including detailed information on dosing, possible side effects, and other interventions.

The grades of evidence (high, moderate, low, very low) are defined at the end of the "Major Recommendations" field.

Who Should Be Tested?

Recommendation 1 The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *Helicobacter pylori* infection. Grade of evidence: not applicable.

Recommendation 2 Diagnostic testing for *H. pylori* infection is not recommended in children with functional abdominal pain. Grade of evidence: high.

Recommendation 3 In children with first-degree relatives with gastric cancer, testing for *H. pylori* may be considered. Grade of evidence: low.

Recommendation 4 In children with refractory iron-deficiency anemia in which other causes have been ruled out, testing for *H. pylori* infection may be considered. Grade of evidence: low.

Recommendation 5 There is insufficient evidence that *H. pylori* infection is causally related to otitis media, upper respiratory tract infections, periodontal disease, food allergy, sudden infant death syndrome (SIDS), idiopathic thrombocytopenic purpura, and short stature. Grade of evidence: low.

Which Diagnostic Test Should Be Applied in Which Situation?

Recommendation 6 For the diagnosis of *H. pylori* infection during esophagogastroduodenoscopy (EGD), it is recommended that gastric biopsies (antrum and corpus) for histopathology are obtained. Grade of evidence: moderate.

Recommendation 7 It is recommended that the initial diagnosis of *H. pylori* infection be based on either positive histopathology + positive rapid urease test or a positive culture. Grade of evidence: moderate.

Recommendation 8 The ^{13}C-urea breath test (UBT) is a reliable noninvasive test to determine whether *H. pylori* has been eradicated. Grade of evidence: high.

Recommendation 9 A validated enzyme-linked immunosorbent assay (ELISA) for detection of *H. pylori* antigen in stool is a reliable noninvasive test to determine whether *H. pylori* has been eradicated. Grade of evidence: moderate.

Recommendation 10 Tests based on the detection of antibodies (immunoglobulin G [IgG], immunoglobulin A [IgA]) against *H. pylori* in serum, whole blood, urine, and saliva are not reliable for use in the clinical setting. Grade of evidence: high.

Recommendation 11 It is recommended that clinicians wait at least 2 weeks after stopping proton pump inhibitor (PPI) therapy and 4 weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (UBT, stool test) for *H. pylori*. Grade of evidence: high.

Who Should Be Treated?

Recommendation 12 In the presence of *H. pylori*–positive peptic ulcer disease (PUD), eradication of the organism is recommended. Grade of evidence: high.

Recommendation 13 When *H. pylori* infection is detected by biopsy-based methods in the absence of PUD, *H. pylori* treatment may be considered. Grade of evidence: low.

Recommendation 14 A "test and treat" strategy is not recommended in children. Grade of evidence: moderate.

Which Treatment Should Be Applied in Which Situation?

Recommendation 15 In children who are infected with *H. pylori* and whose first-degree relative has gastric cancer, treatment can be offered. Grade of evidence: low.

Recommendation 16 Surveillance of antibiotic resistance rates of *H. pylori* strains in children and adolescents is recommended in different countries and geographic areas. Grade of evidence: not applicable.

Recommendation 17 First-line eradication regimens are the following: triple therapy with a PPI + amoxicillin + imidazole; or PPI + amoxicillin + clarithromycin; or bismuth salts + amoxicillin + imidazole; or sequential therapy. Grade of evidence: moderate.

Recommendation 18 Antibiotic susceptibility testing for clarithromycin is recommended before initial clarithromycin-based triple therapy in areas/populations with a known high resistance rate (>20%) of *H. pylori* to clarithromycin. Grade of evidence: moderate.

Recommendation 19 It is recommended that the duration of triple therapy be 7 to 14 days. Costs, compliance, and adverse effects should be taken into account. Suggested doses are given in Table 1 of the original guideline document. Grade of evidence: moderate.

Recommendation 20 A reliable noninvasive test for eradication is recommended at least 4 to 8 weeks following completion of therapy. Grade of evidence: low.

Recommendation 21 If treatment has failed, there are 3 options recommended:

1. EGD, with culture and susceptibility testing, including alternate antibiotics if not performed before guide therapy.
2. Fluorescence in situ hybridization (FISH) on previous paraffin-embedded biopsies if clarithromycin susceptibility testing has not been performed before guide therapy.
3. Modify therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing dose and/or duration of therapy.

Grade of evidence: not applicable.

Definitions:

Grades of Evidence

1. High: Further research is unlikely to change confidence in the estimate of effect.
2. Moderate: Further research is likely to have an important influence on confidence in the estimate of effect and may change the estimate.
3. Low: Further research is very likely to have an important influence on confidence in the estimate of effect and may change the estimate.
4. Very low: Any estimate of effect is uncertain.

Not applicable: The grades of evidence were not relevant for a particular statement.

Clinical Algorithm(s)

A proposed algorithm of how to treat *Helicobacter pylori* infection in pediatric patients is provided in the original guideline document.

Scope

Disease/Condition(s)

- *Helicobacter pylori* infection
- *H. pylori*-associated diseases

Guideline Category

Diagnosis

Evaluation

Screening

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Infectious Diseases

Pathology

Pediatrics

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To improve the care of children and adolescents with *Helicobacter pylori* infection
- To update recommendations for children and adolescents in North America and Europe

Target Population

Children living in Europe and North America with *Helicobacter pylori* infection and complications from infection

Note: These guidelines do not apply to those living in other continents, particularly in developing countries with a high *H. pylori* infection rate in children and adolescents and with limited resources for health care.

Interventions and Practices Considered

Diagnosis/Assessment

1. Invasive tests for *Helicobacter pylori* requiring endoscopy
    - Biopsy and histology
    - Rapid urease testing
    - Bacterial culture
2. Noninvasive tests for *H. pylori*
    - Stool test for *H. pylori* antigen (enzyme-linked immunosorbent assays [ELISAs])
    - ^{13}C-Urea breath testing (UBT)

Treatment

1. Three or four medications given once or twice daily, for one to two weeks.
2. First-line options:
    - Proton pump inhibitor (PPI) + amoxicillin + metronidazole
    - PPI + amoxicillin + clarithromycin
    - Bismuth subsalicylate (or subcitrate) + amoxicillin + metronidazole
    - PPI + amoxicillin + clarithromycin + metronidazole
3. Management following treatment failure
    - Esophagogastroduodenoscopy (EGD), with culture and susceptibility testing, including alternate antibiotics
    - Fluorescence in situ hybridization (FISH) on previous paraffin-embedded biopsies (if clarithromycin susceptibility testing has not been performed)
    - Modification of therapy (addition of an antibiotic, different antibiotics, addition of bismuth, and/or increasing dose and/or duration of therapy)
4. Noninvasive testing for eradication following completion of treatment

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Positive predictive value of diagnostic tests
- Causal relationship between symptoms and *Helicobacter pylori* infection
- Incidence of *H. pylori* infection in children with infected first-degree relatives
- *H. pylori* eradication rate with treatment
- Rate of development of *H. pylori* resistance with treatment
- Treatment side effects

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic literature search was designed by an epidemiologist using accessible databases of relevance: PubMed, MEDLINE, EMBASE, Cochrane Library, Biosis Previews, EBM Reviews, ISI Web of Science, and Scopus. The search included publications from 2000 to August 2007. The search included publications of all types presenting or reviewing data on *Helicobacter pylori* in patients younger than 20 years old, selecting on Medical Subjects Headings (MeSH) terms as listed below, with no language restrictions:

Search Strategy

1. *Helicobacter pylori*
2. *Helicobacter* infection
3. *pylori*
4. or/1–3
5. Newborn
6. Infant
7. Child
8. Adolescent
9. Pediatrics
10. or/5–9
11. 4 and 10
12. 11 and py=2005:2006
13. Limit 12 to human

The search identified 1979 unique publications and an additional 63 publications were generated from the citations of relevant reviews. Of these 2042 papers, the following were excluded: 800 that did not present evidence on relevant topics; 635 that did not present evidence for pediatric groups; 40 letters, commentaries, or case reports; 33 abstracts; 25 non–English-language publications that did not present relevant data in an English-language abstract; and 19 nonsystematic reviews. The total number of selected papers was 490, including 80 reviews.

In addition, within each subgroup, the members were asked to search the literature with respect to their topics to add evidence that may have been missed by the search criteria. In particular, this increased inclusion of publications from less widely circulated journals and from non–English-language sources.

In December 2009, an updated systematic literature search was performed including articles published from September 2007 to 2009. A total of 248 new publications were retrieved and reviewed for new evidence, which may have influence on the recommendations, the evidence, or the strength of recommendations compared with the version presented in August 2008 at the World Congress (see the "Description of the Methods Used to Formulate the Recommendations" field).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grades of Evidence

1. High: Further research is unlikely to change confidence in the estimate of effect.
2. Moderate: Further research is likely to have an important influence on confidence in the estimate of effect and may change the estimate.
3. Low: Further research is very likely to have an important influence on confidence in the estimate of effect and may change the estimate.
4. Very low: Any estimate of effect is uncertain.

Not applicable: The grades of evidence were not relevant for a particular statement.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The papers were grouped according to the review focus areas. Summaries of review papers were prepared and tables were constructed to organize key data regarding study, quality, and findings from the original research reports.

Grading of the quality of evidence was performed by epidemiologists and individual group members, according to the classification system of the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=1025), because this is the only grading system in which studies of diagnostic tests can be scored accordingly. The lists of rated articles and synthesis tables were circulated to the subgroups, and the information was expanded or revised upon closer inspection as appropriate.

Methods Used to Formulate the Recommendations

Expert Consensus

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Selection of Topics and Patients

In 2005, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) decided independently to renew their guidelines, this time with a joint evidence-based methodology. The councils of both societies decided in 2006 that the process should be combined to have the same recommendations for North America and Europe.

The following 4 areas were identified and covered by 4 subgroups, which formulated the critical questions for each area:

1. Who should be tested? (differentiating among screening, surveillance, and clinically based testing)
2. What tests should be used?
3. Who should be treated?
4. What treatment regimens are most appropriate?

An international panel of 11 pediatric gastroenterologists, 2 epidemiologists, 1 microbiologist, and 1 pathologist was selected by societies that developed evidence-based guidelines based on the Delphi process with anonymous voting in a final face-to-face meeting. Each society assigned 1 chair. At least 2 members from each society were assigned to the subgroups for the 4 areas of interest. Members were mostly pediatric gastroenterologists, but experts in epidemiology, microbiology, and pathology were also selected based on their peer-reviewed publications, research activities in the field, and participation in national or international activities. The European patients were recruited from the Pediatric Task Force on *Helicobacter pylori* Infection (ESPGHAN Working Group on *H. pylori*) and also included a representative from the European Helicobacter Study Group.

Voting on Consensus Statements and Grading the Statements for Quality of Evidence

In preparation for a meeting in December 2007 in Munich, Germany, each subgroup had formulated the statements circulated to each member of the subgroups. In addition, the European members of the 4 subgroups presented the statements during the annual meeting of the ESPGHAN Pediatric Task Force in October 2007 in Istanbul, Turkey, where they were extensively discussed and adapted according to the comments of the attendees.

At the meeting in Munich, the group voted on 2 iterations of each of the consensus statements. Statements were revised based on feedback provided from the patients and further critical review of the available literature. Some of the statements were deleted by voting and the content of these was condensed into comments pertaining to relevant statements that remained. Additional statements were added on matters that had not been addressed previously.

All of the votes were anonymous. A 6-point scale was used: 1, agree strongly (A+); 2, agree moderately (A); 3, just agree (A–); 4, just disagree (D–); 5, disagree moderately (D); and 6, disagree strongly (D+). Agreement with the statement (the sum of voting for A+, A, or A–) by three-quarters (i.e., ≥75%) of the voting members was defined a priori as consensus. The level of agreement in the final vote is provided for each statement, expressed as a percentage.

Grades of evidence for each statement were based on the grading of the literature and were finally assigned using the Grading Recommendations Assessment, Development and Evaluation (GRADE) system of 2004 (see the "Rating Scheme for the Strength of the Evidence" field).

The designation "not applicable" was used for situations in which these grades of evidence were not relevant for a particular statement.

Consensus Meeting

Seven North American members (4 from the United States, 2 from Canada, 1 from Mexico) and 8 European members attended the final meeting. One attendee, who was not eligible to vote, observed and documented the voting process, which was later compared with the recorded electronic voting slides. The statements were presented at the World Congress of Pediatric Gastroenterology in Iguassu Falls, Brazil, on August 19, 2008 to the scientific community and feedback was requested. The first-draft manuscript was prepared by the chair of the European group in collaboration with a member of the North American group and the 2 epidemiologists. Because of a change in the NASPGHAN chair, the manuscript was on hold for 18 months. In December 2009, an updated systematic literature search was performed (see the "Description of Methods Used to Collect/Select the Evidence" field). The new literature was implemented in the final draft, which then was circulated to all members of the consensus group and their input was worked into the manuscript.

Statements

For the first round of voting, 43 statements were presented and agreement was reached for 22 of them. Several statements were omitted, some combined into 1, and others reworded after discussion. There were 21 statements in the final round of voting, and consensus was reached for all of them. The result of the final voting is provided for every statement (see the original guideline document).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

- The statements were presented at the World Congress of Pediatric Gastroenterology in Iguassu Falls, Brazil, on August 19, 2008 to the scientific community and feedback was requested.

- Members of the Gastrointestinal (GI) Committee of European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) critically reviewed the manuscript.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate diagnosis and treatment of *Helicobacter pylori* in the pediatric population
- Eradication of *H. pylori* in infants, children, and adolescents

Potential Harms

- Potential development of *Helicobacter pylori* antibiotic resistance
- Adverse effects of medications
- False-positive or false-negative results of tests

Qualifying Statements

Qualifying Statements

- These clinical practice guidelines represent updated, best-available evidence and are meant for children and adolescents living in Europe and North America, but they may not apply to those living on other continents, particularly in developing countries with a high *Helicobacter pylori* infection rate and limited health care resources.
- The guidelines may need to be adapted to national health care systems because certain tests or treatment regimens may not be available and/or reimbursed by health insurance programs.
- As the clinical implications of *H. pylori* infection in the pediatric setting continue to evolve, these guidelines will need to be updated.
- A crucial question for all tests performed in a pediatric population is whether the accuracy of the applied method is influenced by the age of the tested child. It is necessary to consider different age groups: infants, toddlers, preschool-age and school-age children, and adolescents. Most of the validation studies in children included only a few *H. pylori*–infected infants and toddlers. Therefore, the information with respect to sensitivity is limited in these age groups.
- The decision to treat *H. pylori*-associated gastritis without duodenal or gastric ulcer is subject to the judgment of the clinician and deliberations with the patient and family, taking into consideration the potential risks and benefits of the treatment in the individual patient.
- A recent meta-analysis of eradication treatment efficacy in children concluded that, in general, the methodological quality of the studies was poor and that additional well-designed randomized trials are needed. Thus, current recommendations remain mainly extrapolated from adult studies.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2000 Nov (revised 2011 Aug)

Guideline Developer(s)

European Society for Pediatric Gastroenterology, Hepatology, and Nutrition - Professional Association

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition - Professional Association

Source(s) of Funding

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Guideline Committee

H pylori Working Groups of the (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) ESPGHAN and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)

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Financial Disclosures/Conflicts of Interest

The authors report no conflicts of interest other than those reported on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Web sites.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) and EPUB from the Journal of Pediatric Gastroenterology and Nutrition Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on June 9, 2003. The information was verified by the guideline developer on June 16, 2003. This

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